Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and correlation with cognitive function

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Abstract

Objectives To compare the prevalence of silent cerebral ischemia (SCI) and cognitive performance in paroxysmal and persistent atrial fibrillation (AF) patients and controls in Sinus Rhythm (SR).

Background Large registries reported a similar risk for symptomatic stroke in both paroxysmal and persistent AF. The relationship between paroxysmal and persistent AF, SCI and cognitive impairment has remained uncharted.

Methods and results Two hundred-seventy subjects were enrolled: 180 patients with AF (50% paroxysmal and 50% persistent) and 90 controls. All subjects received clinical assessment, neurological examination, cerebral magnetic resonance (MR) and underwent the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). At least one SCI was present in 80 (89%) patients with paroxysmal, 83 (92%) with persistent AF (paroxysmal vs persistent; p=0.59) and in 41 (46%) controls (paroxysmal vs controls and persistent vs controls; p<0.01). Number of SCI per person was higher in persistent than in paroxysmal AF patients (41.1±28.0 vs 33.2 ±22.8; p=0.04), with controls reporting lower figures (12.0±26.7; both p<0.01). Cognitive performance was significantly worse in persistent and paroxysmal AF patients than in controls (RBANS 82.9±11.5, 86.2±13.8 and 92.4±15.4 points respectively; p<0.01).

Conclusions Paroxysmal and persistent AF patients presented a higher prevalence and number of SCI per patient than controls and confirmed a worse cognitive performance than subjects in SR.

List of abbreviations

Atrial Fibrillation (AF)

Silent Cerebral Ischemia (SCI)

Computed Tomography (CT)

Magnetic Resonance (MR)

Transient Ischemic Attack (TIA)

Mini Mental State Evaluation (MMSE)

Beck Depression Inventory (BDI)

CHA_2DS_2-Vasc: congestive heart failure/left ventricular dysfunction; hypertension; age; diabetes; stroke/transitory ischemic attack, thromboembolism; vascular disease

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

T2 fluid-attenuated Inversion Recovery (T2 FLAIR)

Diffusion-Weighted (DW)

Analysis of Variance (ANOVA)

Confidence Intervals (CI)

Odds Ratio (OR)

Introduction

Atrial fibrillation (AF) is known to relate, independently from the presence of other comorbidities, to enhanced mortality and thromboembolism (1), particularly to the brain. To date large registries have reported a similar risk for symptomatic stroke in both the paroxysmal and the persistent form of this arrhythmia (2ï 4). A recent clinical experience on patients with acute cerebral infarction suggested, however, that patients with persistent AF present a significantly worse short-term outcome both in functional ability and survival respect to those with paroxysmal AF (5).

If symptomatic brain damage is easily diagnosed, the relationship between AF, both paroxysmal and persistent, and silent cerebral ischemia (SCI) has remained uncharted. The presence of SCI is of relevant interest as it was associated to increased occurrence of stroke (6) and development of cognitive impairment (7, 8).

Few studies (9ï 13) have, in fact, investigated the prevalence of SCI in patients with AF. The limited sample size, the retrospective design, or the heterogeneity of patients and techniques (e.g. computed tomography, CT vs magnetic resonance, MR) involved in these studies explain the broad variations reported from 15% to 86%. In addition the relationship between paroxysmal and persistent AF and cognitive decline has, to date, relied only on clinical data, not supported by cerebral imaging (14ï 17).

Aims of the present study are to compare: 1) prevalence of SCI and 2) cognitive performance in paroxysmal and persistent non valvular AF patients and in controls in sinus rhythm (SR), without history of AF.

Methods

Study population

From November 2008 to September 2012 consecutive patients referred to our Cardiology Division or Cardiovascular Prevention Outpatient Clinic were screened to generate three age, gender, risk factors and education level-balanced groups of patients with paroxysmal or persistent AF or without history of AF.

Exclusion criteria were: valvular heart disease, acute coronary syndrome less than 3 months before, previous transcatheter ablation, pace-maker implantation or other MR contraindications, history of transient ischemic attack (TIA) or stroke, autoimmune diseases, inflammatory brain diseases, tumors, severe hepatic disorders, severe chronic renal insufficiency and alcohol abuse.

All patients were screened by the Mini Mental State Evaluation (MMSE) (18) and the Beck Depression Inventory (BDI) scale (19) to rule out dementia or depression. Participants with scores Ò24 points on the MMSE and Ó10 on the BDI were excluded.

Flow chart reporting numbers and reasons of exclusion of the screened cohort down to the final study population is reported in Figure 1.

The final study population enrolled 270 subjects: 180 patients with AF, 90 paroxysmal and 90 persistent and 90 controls in SR without history of AF. AF was defined paroxysmal if self-terminating within 7 days and persistent if at least one AF episode lasted longer than 7 days, based on direct patient interview and/or exhaustive medical papers search.

All patients gave written informed consent before enrolment; the study was conducted in accordance to the latest Declaration of Helsinki and approved by the Local Ethical Committee.

Baseline evaluation

All screened subjects underwent extensive clinical assessment, including: medical history (targeted to AF type and duration, presence of heart disease, comorbidities), thromboembolic risk assessment (CHA_2DS_2-Vasc score, congestive heart failure/left ventricular dysfunction; hypertension; age; diabetes; stroke/transitory ischemic attack, thromboembolism; vascular disease) (20), physical examination and electrocardiogram. Hypertension was defined as blood pressure Ó140/90 mmHg (grade 1 hypertension: 140-159/90-99 mmHg, grade 2 hypertension 160-179/100-109 (21). Diabetes was defined as HbA1c Ó6.5% (22). Hypercholesterolemia was considered in case of evidence of a total cholesterol blood sample above 240 mg/dl (23). Smoking was considered habitual if the patient smoked at least 20 cigarettes a day for at least 1 year.

A standardized neurological examination, according to the National Institute of Health Stroke Scale, was performed by a certified neurologist. In addition, all patients underwent Echo-Doppler sonography to exclude carotid and vertebro-basilar district morphological and/or functional damage (stenosis of the lumen Ó70%, according to European Carotid Surgery Trial criteria or a peak systolic flow velocity > 150 cm/sec).

Cognitive performance

Cognitive function was assessed by a certified neuropsychologist with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (24, 25) exploring 5 domains: immediate memory, visual-spatial abilities, language, attention and delayed memory.

Magnetic resonance imaging

Cerebral images were obtained with an 8-channel head coil 1.5 Tesla MR imaging system (Magneton Avanto®, Siemens, Erlangen, Germany). The imaging protocol included: a sagittal T1-weighted spin echo sequence (repetition time/echo time 400/13; slice thickness 5 mm; field of view 230 mm; matrix 192x256), an axial T2 fluid-attenuated inversion recovery (T2 FLAIR) weighted sequence (repetition time/echo time 8500/112; TI 2500 ms; slice thickness 5 mm; field of view 240 mm; matrix 154x256; seconds) and a diffusion-weighted (DW) sequence (repetition time/echo time 3200/99; slice thickness 5 mm; field of view 230 mm; matrix 128%128; bandwidth 1502 Hz; gradient strength 22 mT; duration of diffusion gradients 31 ms; gradient separation 42 ms in 3 orthogonal directions, B value 1000). For each DW sequence, the apparent diffusion coefficient map was obtained. All sequences were centered on the axis defined by a line passing between the anterior and posterior cerebral commissures.

According to anatomo-pathological criteria (26), SCI were defined as focal, sharply demarcated, regularly or irregularly shaped areas hyperintense on T2 FLAIR or isointense in T1 weighted images. T2 FLAIR were used to differentiate gliotic ischemic lesions smaller than 3 mm from perivascular spaces and lacunes (hypointense on T2 FLAIR weighted images) (27).

The presence of even only one lesion allocated the subject within the SCI group. Each individual SCI was recorded and small lesions closely grouped together, exclusively localized in the subcortical white matter of the frontal lobe, were defined as ñspotted patternò.

All MR scans were independently analyzed by two neuroradiologists, blinded to clinical data; conflict was resolved by common agreement referring to a third expert.

Statistical analysis

Continuous variables, presented as means and standard deviations (SD), were compared by analysis of variance (ANOVA) and subgroup comparisons corrected by the post-hoc Bonferroniôs correction. Categorical variables, presented as counts and percentages, were compared in cross tabulation tables by chi square test (Yatesôs correction, as appropriate) and Odds Ratio (OR) with their 95% confidence intervals (95% CI) computed. A logistic regression model was performed to determine the correlation between SCI and potential confounders selected at univariate analysis ($p<0.5$). All analyses were performed by the SPSS package for Windows (v. 18.0, SPSS Inc, Chicago, IL, USA) and a p value below 0.05 was considered as statistically significant.

Results

Baseline characteristics of the final patient population are summarized in Table 1.

Silent cerebral ischemia

At least one SCI was present in 80 (89%) patients with paroxysmal AF, 83 (92%) with persistent AF (paroxysmal vs persistent AF; $p = 0.59$) and in 41 (46%) controls (paroxysmal vs controls and persistent vs controls; $p < 0.01$).

Cerebral lesions were bilateral in 81 (90%) persistent and 80 (89%) paroxysmal AF patients ($p = 1$) compared to 36 (40%) within controls (paroxysmal vs controls and persistent vs controls; both $p<0.01$). SCI were cortical and subcortical in 75 (83%) and 77 (85%) paroxysmal AF patients, in 79 (88%) and 82 (91%) persistent AF patients and in 19 (21%) and 44 (49%) within controls,

respectively (paroxysmal vs persistent AF; p = 0.5 and p = 0.35; AF patients vs. controls; p < 0.01).

The number of SCI per person was significantly higher in persistent than in paroxysmal AF patients (41.1 ± 28.0 vs 33.2 ± 22.8; p = 0.04). The number of SCI per person was significantly higher in paroxysmal and in persistent AF patients than in controls, reporting lower figures (12.0 ± 26.7; paroxysmal vs controls and persistent vs controls; both p < 0.01). AF showed a higher risk for SCI respect to subjects in SR [OR, Odds Ratio = 11.2 (6-21); p < 0.01] whereas no difference was found between the two different forms of the arrhythmia [OR=1.5 (0.5-4.1); p = 0.61]. At multivariate analysis, adjusted for age, CHA2DS2-Vasc score and antiplatelet/oral anticoagulation treatment, the presence of AF was strongly independently related to the presence of SCI (OR 7.2, 95%CI 2,3-22,3; p=0.001).

The prevalence of ñspotted patternò in the frontal lobe was more represented in persistent than in paroxysmal AF (67% vs 50%; p = 0.03). In controls the presence of this patterns was negligible (1%).

Cognitive function

Cognitive performance, assessed by RBANS, was significantly worse in persistent and paroxysmal AF patients than in controls: 82.9 ± 11.5, 86.2 ± 13.8, and 92.4 ± 15.4 points, respectively (paroxysmal vs persistent AF; p = 0.08; paroxysmal and persistent AF vs controls; p < 0.01). In details, AF patients obtained lower mean scores than controls in all the explored domains: immediate memory, visual-spatial abilities, language, attention and delayed memory (Figure 2). Concerning AF type, persistent AF patients presented a trend toward lower RBANS scores mainly driven by significantly worse visual-spatial abilities (84.8 ± 14.8 vs 89.9 ± 18.2; p

= 0.04) compared to patients with the paroxysmal form of the arrhythmia.

Among AF patients, those with the frontal pattern (58%) presented a trend toward a lower mean total score compared to those without (82.9 ± 12.0 vs 86.5 ± 15; p = 0.06). However, they scored significantly lower in visual-spatial ability subtest respect to subjects without this pattern (85.1 ± 16.7 vs 90.7 ± 17; p = 0.02).

Discussion

The present is, to the best of our knowledge, the first study investigating the relationship between AF and cognitive decline supported by specifically addressed cerebral MR imaging.

The major findings of this study are:

1) AF patients (both paroxysmal and persistent) present higher prevalence but, most of all, number of SCI per person compared to controls;
2) persistent relates to higher SCI per person compared to paroxysmal AF;
3) AF patients have a worse cognitive performance compared to controls;
4) despite similar cognitive function by RBANS between paroxysmal and persistent AF patients, visual-spatial abilities were worse in persistent AF.

The incidence of clinical ischemic stroke has been reported as up to five-fold higher in AF patients compared to the general population (2, 3, 28). Similarly the present study including subjects with homogenous cardiovascular risk factors by study design reported a higher risk of SCI in AF patients compared to subjects in SR.

The high prevalence of SCI within controls (46%), compared to that reported in the general population (29, 30), may relate to the baseline characteristics of this group. Due to their selection within patients referring to a Cardiovascular Prevention Outpatient Clinic, the control group presented a moderate to high cardiovascular risk profile. Interestingly, the prevalence of SCI in subjects with similar cardiovascular risk profile in previous experiences ranges from 53 to 58%, similar to that reported in the present study (12, 13, 31).

Besides the higher prevalence of SCI, by discriminating individual lesions in each patient, we registered a higher number of SCI per person in paroxysmal and persistent AF patients compared to controls.

SCI may certainly have both ischemic and embolic origin. The design of the study, comparing AF patients and non-AF controls with similar prevalence of classical cardiovascular factors should, however, permit to focus on the excess due to AF related embolic lesions. Emboli of cardiac origin are generally smaller than those due to atherothrombotic material and cause lesions widely distributed, on both sides, of the brain (9, 32, 33). On the contrary, emboli, for instance of carotid artery origin, are usually larger in size and damage the ipsilateral hemisphere. For these reasons the peculiar cerebral MR pattern described in 50% and 67% of the paroxysmal and persistent AF patients, respectively presenting small sharply demarcated lesions, often in cluster, with bilateral distribution, prevalently in the frontal lobe strongly supports an embolic mechanisms. This pattern is, in fact, clearly distinguishable from an atherosclerotic damage ipsilateral to a vascular lesion. In our opinion, the ñspotted patternò described in this study may derive from microembolization of multiple small platelet thrombi in the terminal brain vessels (especially the leptomeningeal arteries)ò.

Furthermore, although patients with paroxysmal and persistent AF did not present differences in SCI prevalence, persistent AF showed a higher number of lesions. To date, persistent and paroxysmal AF were considered to present similar stroke risk (2ï 4) and studies on symptomatic cerebral damage rarely differentiate between the two clinical forms of the arrhythmia.

This result might be related to the longer presence and duration of AF in the persistent form causing a greater exposure time to AF related thromboembolic etiology. Considering the high clinical impact that this finding may provide it surely warrants further confirmation.

As shown in Table 1 paroxysmal were more commonly prescribed antiaggregant therapy compared to persistent AF patients. This somewhat surprising finding most likely is due to the fact that patients were enrolled between 2008 and 2012. The evidence that aspirin is not

beneficial in AF patients first emerged in 2011 (34). Before this date aspirin was commonly, although not evidence-based, chosen for treatment of patients with paroxysmal episodes.

As suggested by previous researches (16, 17) AF relates to cognitive decline; in particular Santangeli et al. outlined that AF independently increases the risk of incident dementia both in elderly patients without acute stroke and with normal baseline cognitive function.

AF patients performed worse in all investigated cognitive domains compared to subjects without history of AF. Interestingly the score difference highlighted between AF patients and controls relates to a relevant clinical shift from a medium to a medium-low cognitive performance (24).

Overall in our dataset RBANS score and number of SCI were poorly related (Pearson correlation coefficient r=0.185; p=0.02). In our opinion this has two main explanations. First, the loss of neuropsychological and cognitive function deriving from a cerebral lesion depends on its localization and dimension. Differences in cognitive function seem more related to the presence of small clustered lesions in the subcortical frontal region than to the overall number of SCI. Patients with the frontal pattern (58%) presented a clear trend toward lower total scores (82.9 ±12.0 vs. 86.5 ±15; p = 0.06) and, especially, they scored significantly lower in the visual-spatial ability subtests (85.1 ±16.7 vs. 90.7 ±17; p = 0.02) compared to subjects without this pattern. In fact, the frontal subcortical cerebral circuits (35) which could indeed be damaged by the presence, at this level, of the ñspotted patternò are involved in several neurological activities such as visual spatial abilities. Second, the neuropsychological test used in the present study is a first level assessment tool, exploring only a limited selection of cognitive functions. We therefore cannot exclude that the cognitive measures used may in certain cases perform above the detection threshold.

Finally, the anatomical brain damage visible by MR did not remain, from a functional point of

view, really "silent". The present data suggest that an initially limited cerebral damage may become overt as the number of cerebral lesions increases due to persistence of the arrhythmia.

Study limitations

In addition to those reported above the following general limitations apply to this study. The cross sectional study design investigating time dependent risks may represent a source of bias. Future research on this topic should hopefully include longitudinal studies with appropriate power and sample size. Furthermore, as in most studies on this topic, an accurate measurement of the effective period of anticoagulation or antiaggregant therapy during exposure to the arrhythmia is lacking. For these reasons the results of the present study are to be considered as suggestive, and not conclusive, for further research on this clinically relevant topic.

Conclusions

As for symptomatic strokes, AF patients, both paroxysmal and persistent, suffer higher prevalence of AF related silent cerebral ischemia compared to controls in SR. Finally AF patients were confirmed to have a worse cognitive performance than subjects in SR.

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Table 1. Baseline characteristics of atrial fibrillation patients and controls included in the final study population. Values reported as counts and percentage if not differently stated.

Variable	Paroxysmal AF (n = 90)	Persistent AF (n = 90)	Controls (n = 90)	p Value
Age (years)	58.6 ± 10.2	61.2 ± 10.9	59.7± 13.1	0.31
Gender (male)	69 (76.7%)	72 (80%)	68 (75.6%)	0.76
Hypertension	46 (51.1%)	47 (52.2%)	45 (50%)	0.96
grade 1	33 (36.7%)	28 (31.1%)	33 (36.7%)	0.66
grade 2	13 (14.4%)	19 (21.1%)	12 (13.3%)	0.31
on drugs	39 (43.3%)	41 (45.6%)	36 (40%)	0.75
B-Blockers	33 (36.7%)	36 (40%)	27 (30%)	0.36
ACEis*/ARBsÀ	28 (31.1%)	28 (31.1%)	25 (27.8%)	0.85
Diabetes	5 (5.6%)	7 (7.8%)	5 (5.6%)	0.78
Heart disease:	6 (6.7%)	9 (10%)	7 (7.8%)	0.71
coronary artery disease	3 (3.3%)	3 (3.3%)	4 (4.4%)	0.90
hypertrophic cardiomyopathy	1 (1.1%)	2 (2.2%)	1 (1.1%)	0.78
ipokinetic cardiomyopathy	1 (1.1%)	3 (3.3%)	2 (2.2%)	0.60
congenital heart disease	1 (1.1 %)	1 (1.1%)	0 (0%)	0.60
AF duration (months)	84.2±70.4	85.2±91.2	-	0.80
Time since persistent AF (months)	-	15±28	-	
CHA_2DS_2-Vascÿ				
0	27 (30%)	24 (26.7%)	-	0.74

1	34 (37.8%)	24 (26.7%)	-	0.15
2	19 (21.1%)	22 (24.4%)	-	0.72
> 2	10 (11.1%)	20 (22.2%)	-	0.07
Dyslipidemia	26 (28.9%)	21 (23.3%)	24 (26.7%)	0.69
Antiplatelets/OACƐ				
OAC	39 (43.3%)	79 (87.8%)	0 (0%)	< 0.01
Aspirin 100 mg/day	34 (37.8%)	9 (10%)	11 (12.2%)	< 0.01
None	17 (18.9%)	2 (2.2%)	79 (87.8%)	< 0.01
Smoking habit	26 (28.9%)	26 (28.9%)	31 (34.4%)	0.65
Education level§	2.6±0.9	2.6±0.9	2.5 ±1.0	0.71

* ACEis, Angiotensin-converting enzyme inhibitors.

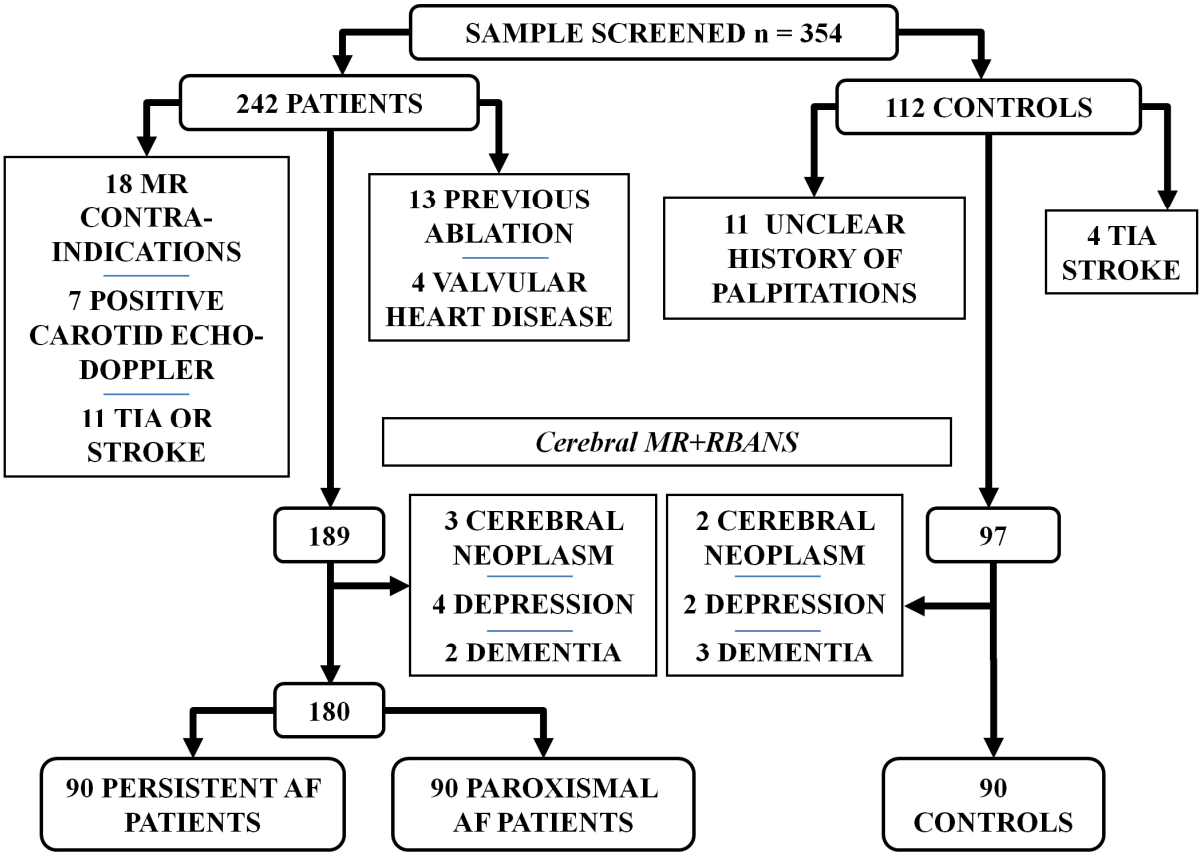
ÀARBs, Angiotensin receptor blockers.

ÿ CHA_2DS_2-Vasc, congestive heart failure/left ventricular dysfunction; hypertension; age; diabetes; stroke/transitory ischemic attack, thromboembolism; vascular disease.

§ Education level: 1, up to 5 school years; 2, up to 8 years; 3, up to 13 years; 4, above 13 years.

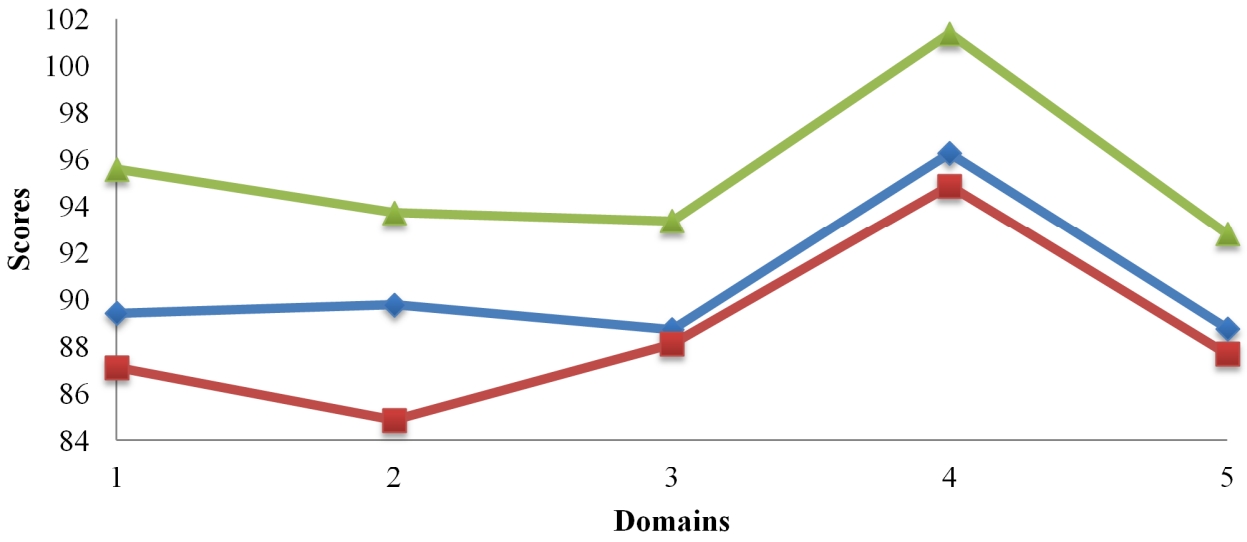
Ɛ OAC, oral anticoagulation.

Figure 1: Flow chart reporting numbers and reasons of exclusion of the screened cohort down to the final study population.



AF, atrial fibrillation; MR, magnetic resonance; RBANS, Repeatable Battery for Assessment of Neuropsychological status; TIA, transitory ischemic attack.

Figure 2: Cognitive function by Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score in controls (triangles), Paroxysmal (PRX, diamonds) and Persistent (PER, squares) AF patients.



	Controls (N = 90)	PRX AF (N = 90)	PER AF (N = 90)	p PRX / controls	p PER / controls	p PRX/ PER
Domains	92.4 ± 15.4	86.2 ± 13.8	82.9 ± 11.5	< 0.01	< 0.01	0.08
1-Immediate Memory	95.6 ± 17.5	89.9 ± 14.7	87.1 ± 16.9	0.02	< 0.01	0.24
2-Visuo-spatial abilities	93.8 ± 16.7	89.9 ± 18.2	84.8 ± 14.8	0.14	< 0.01	0.04
3-Language	92.9 ± 11.4	88.8 ± 9.1	88.1 ± 8.7	< 0.01	< 0.01	0.59
4-Attention	101.4 ± 21.2	96.6 ± 16.6	94.9 ± 15.6	0.09	0.02	0.47
5-Delayed memory	93.5 ± 11.7	88.7 ± 14.7	87.7 ± 14	0.02	< 0.01	0.64

Figure 3: 55 years-old male with paroxysmal atrial fibrillation without other risk factors: axial FLAIR images demonstrate multiple small hyperintense lesions at the subcortical level in both hemispheres. Clusters (arrows) of small lesions are visible in the left frontal and temporo-parietal regions (A), in the left frontal (B) and in the right frontal lobe (C).